The Value of Smoking Cessation and CHANTIX® (varenicline) Coverage

Please see full Prescribing Information and Medication Guide on the following pages.

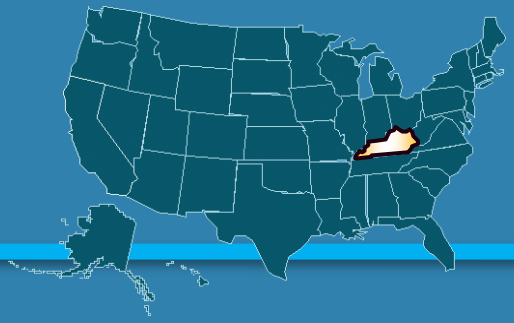
The Value of Providing Smoking Cessation Coverage

Key Objectives

- Understand cigarette smoking as a significant health issue
- Assess the economic burden of smoking
- Illustrate the growing recognition of the value of smoking cessation
- Agree that smoking is a chronic, relapsing medical condition
- Demonstrate the significant health benefits of smoking cessation
- Examine current smoking cessation therapies
- Review CHANTIX® (varenicline) efficacy and updated safety profile
- Communicate elements of the GETQUIT® behavioral modification program
- Outline the economic value considerations for payers of CHANTIX
- Review leading practices in providing a smoking cessation benefit

Please see full Prescribing Information and Medication Guide on the following pages.

Smoking Statistics for Kentucky

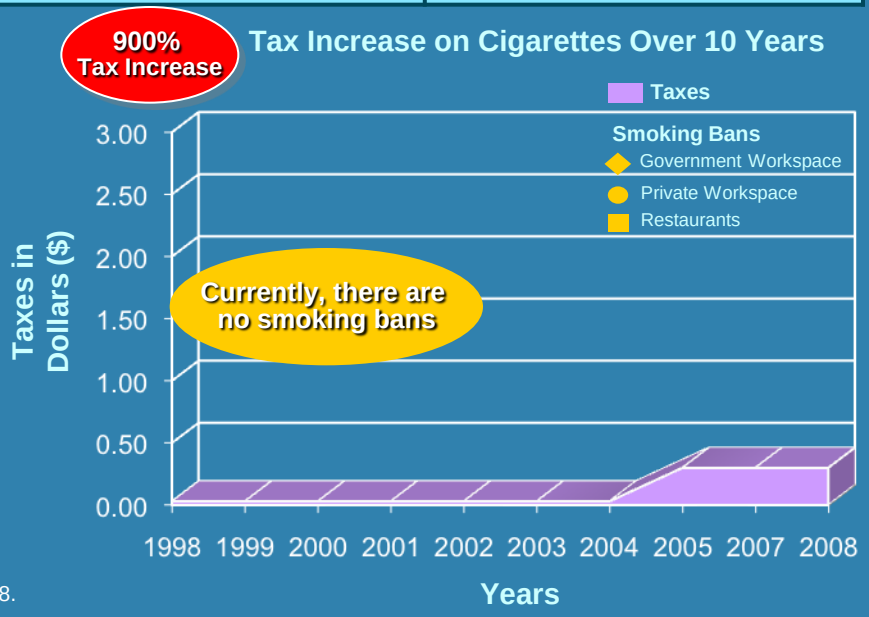


2007 National Average: 20%

Smoking Prevalence	Total Medical Costs (per 100,000 lives)	Productivity Costs (per 100,000 lives)
28.3%	$35,365,064	$50,407,005

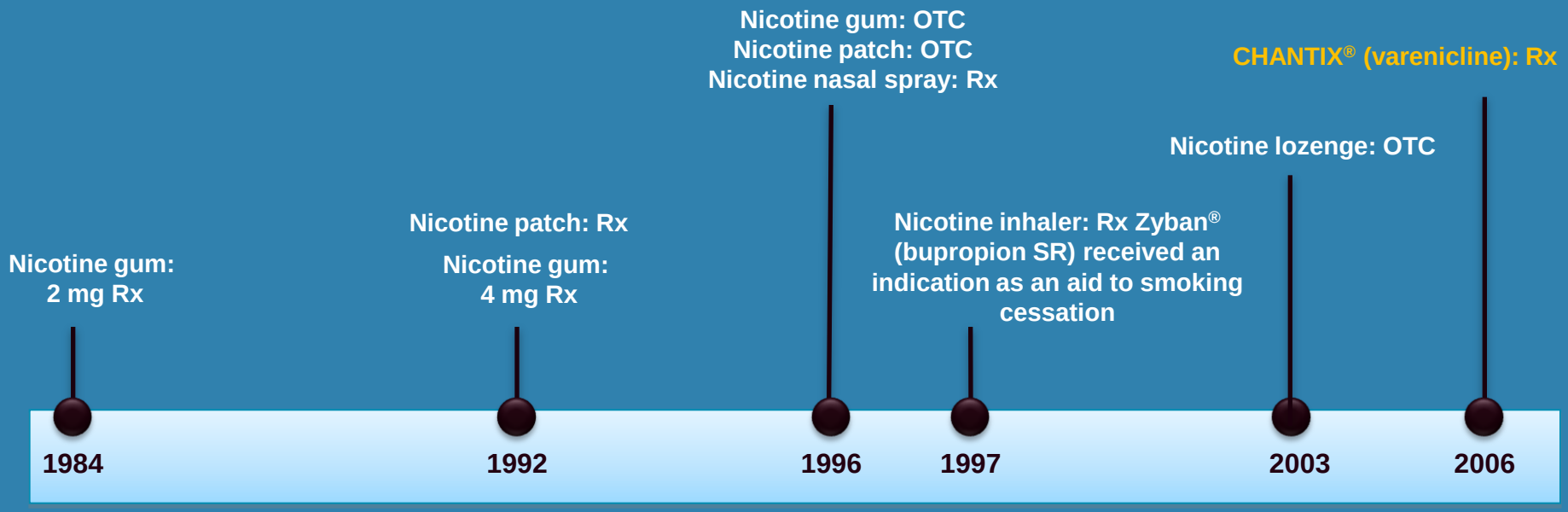
Cost of Cigarettes….$3.46 (per pack)

Excise Tax on Cigarettes…..$0.30 (per pack)



CDC. http://apps.nccd.cdc.gov/StateSystem/systemindex.aspx. Accessed August 19, 2008.
CDC. *MMWR Morb Mortal Wkly Rep*. 2008;57:1221-1226.
CDC. http://apps.nccd.cdc.goc/StateSystem/systemindex.aspx. Accessed August 19, 2008.
CDC. http://apps.nccd.cdc.gov/SateSystem/system index.aspx. Accessed August 19, 2008.
CDC. http://www.cdc.gov/tobacco/data_statistics/state_data/data_highlights/2006/00_pdfs/DataHighlights06table4.pdf. Accessed August 19, 2008.
US Census Bureau. http://factfinder.census.gov/servlet/DatasetMainPageServlet?_ program=PEP. Accessed August 19, 2008.
CDC. http://apps.nccd.cdc.gov/StateSystem/systemindex.aspx. Accessed August 19, 2008.
CDC. http://apps.nccd.cdc.gov/StateSystem/systemindex.aspx. Accessed August 19, 2008.
CDC. http://apps.nccd.cdc.gov/StateSystem/systemIndex.aspx. Accessed August 19, 2008.

Approval Dates for Smoking Cessation Therapies



- NRTs were the first medications approved by the FDA for smoking cessation, followed by sustained-release bupropion
- Currently, there are 5 forms of NRT available in the United States
- Before the approval of CHANTIX in 2006, it had been nearly a decade since the approval of anotherprescription pharmacotherapy for smoking cessation

FDA=Food and Drug Administration.
NRT=nicotine replacement therapy.
Zyban is a registered trademark of GlaxoSmithKline.
Cummings KM et al. *Annu Rev Public Health*. 2005;26:583-599.
FDA Center for Drug Evaluation and Research. http://www.fda.gov/cder. Accessed June 9, 2006.
Please see full Prescribing Information and Medication Guide on the following pages.

Standard Efficacy Measures Utilized in Smoking Cessation Trials

- Point prevalence of abstinence (PPA)
  - Defined as not smoking (not even a puff) for a specified period leading up to a single point of follow-up
  - The majority of clinical trials in the past have used a 7-day PPA
- Continuous abstinence rate (CAR)
  - Defined as not smoking (not even a puff) throughout the specified period of follow-up and is measured at multiple time points
  - Because the specified length of time that an individual needs to remain abstinent is generally weeks to months, it is a stringent criterion for abstinence

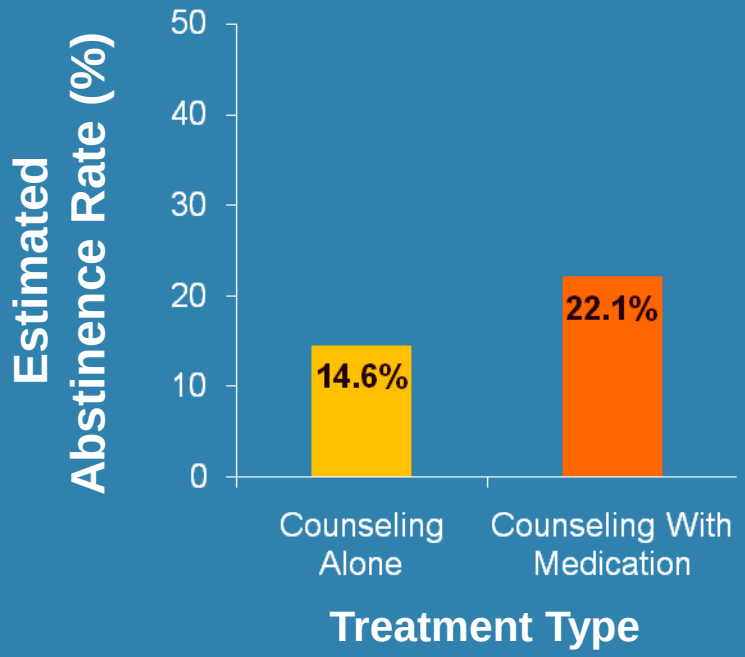
CHANTIX® (varenicline) studies' primary efficacy end point was 4 week CAR, whereas many other studies used a 7-day PPA

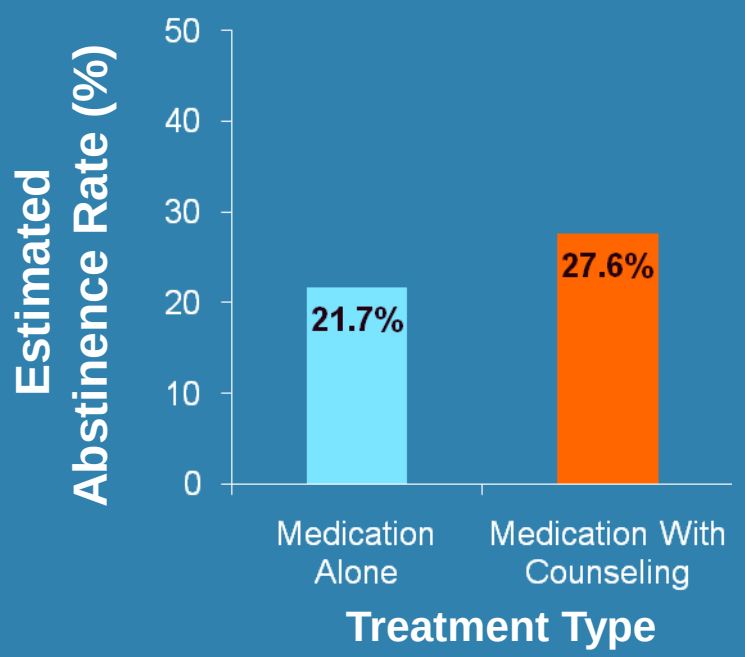
Gonzales D et al. *JAMA*. 2006;296:47-55.

Please see full Prescribing Information and Medication Guide on the following pages.

According to 2 Different Meta-Analyses, a Combination of Counseling and Medication Is More Successful Than Using Either Alone

Comparative Effectiveness of Smoking Cessation Treatments





By combining medication and counseling, the clinician can improve abstinence rates.

Fiore MC et al. Rockville, MD: USDHHS. PHS. May 2008.
Molyneux A et al. *Thorax*. 2003;58(6):484-488.
Ockene JK et al. *J Gen Intern Med.* 1991;6:1-8.
Solomon LJ et al. *Prev Med.* 2000;31:68-74.
Lancaster T et al. *The Cochrane Library*. 2008;4:8.
Stead LF et al. *The Cochrane Library*. 2008;4:11,136-146.

CHANTIX® (varenicline): The Power to Help Them Quit

Please see full Prescribing Information and Medication Guide on the following pages.

CHANTIX® (varenicline): Deliberate Drug Discovery

Deliberate Drug Discovery

- Specifically designed for smoking cessation treatment
- 10 years were invested to develop a product to meet this need
- CHANTIX molecule was first synthesized at Pfizer, in February 1997

When introduced, CHANTIX offered a new way to assist smoking cessation

- CHANTIX contains no nicotine, but targets the same receptors that nicotine does
- CHANTIX is believed to block nicotine from these receptors
- CHANTIX has both a partial-agonist and antagonist effect

Coe JW et al. *Bioorg Med Chem Lett*. 2005;15(12):2974-2979.

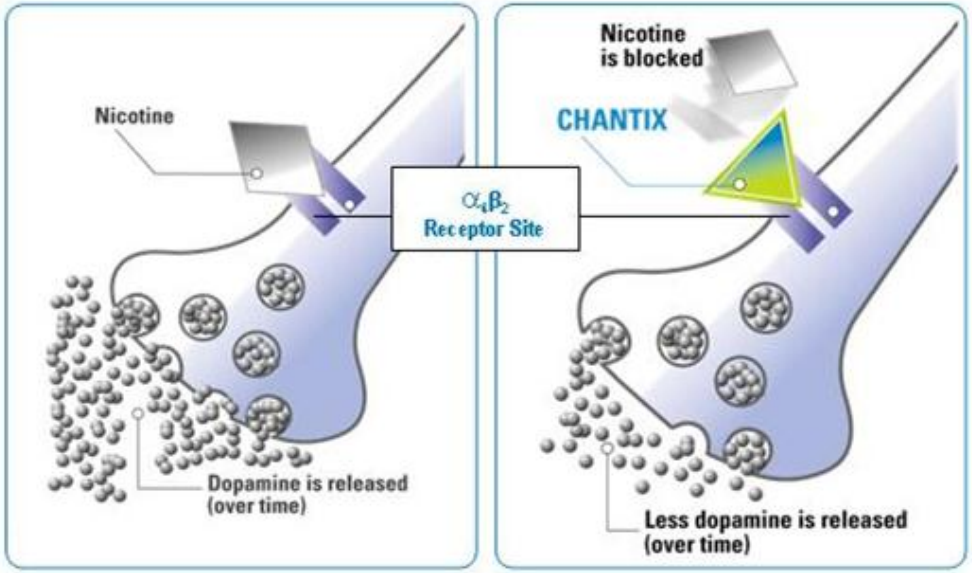
Please see full Prescribing Information and Medication Guide on the following pages.

CHANTIX® (varenicline): Dual Action for Smoking Cessation

The efficacy of CHANTIX in smoking cessation is believed to be the result of varenicline's mechanism of action (MOA)

NICOTINE
AGONIST ACTION

FULL AGONIST EFFECT:
Nicotine (eg, from smoking or nicotine replacement therapy) binds to receptors, stimulating the release of dopamine



CHANTIX
DUAL ACTION

AGONIST EFFECT:
CHANTIX, a non-nicotine agent, binds to receptors, resulting in a limited release of dopamine.

ANTAGONIST EFFECT:
CHANTIX blocks nicotine from binding to receptors.

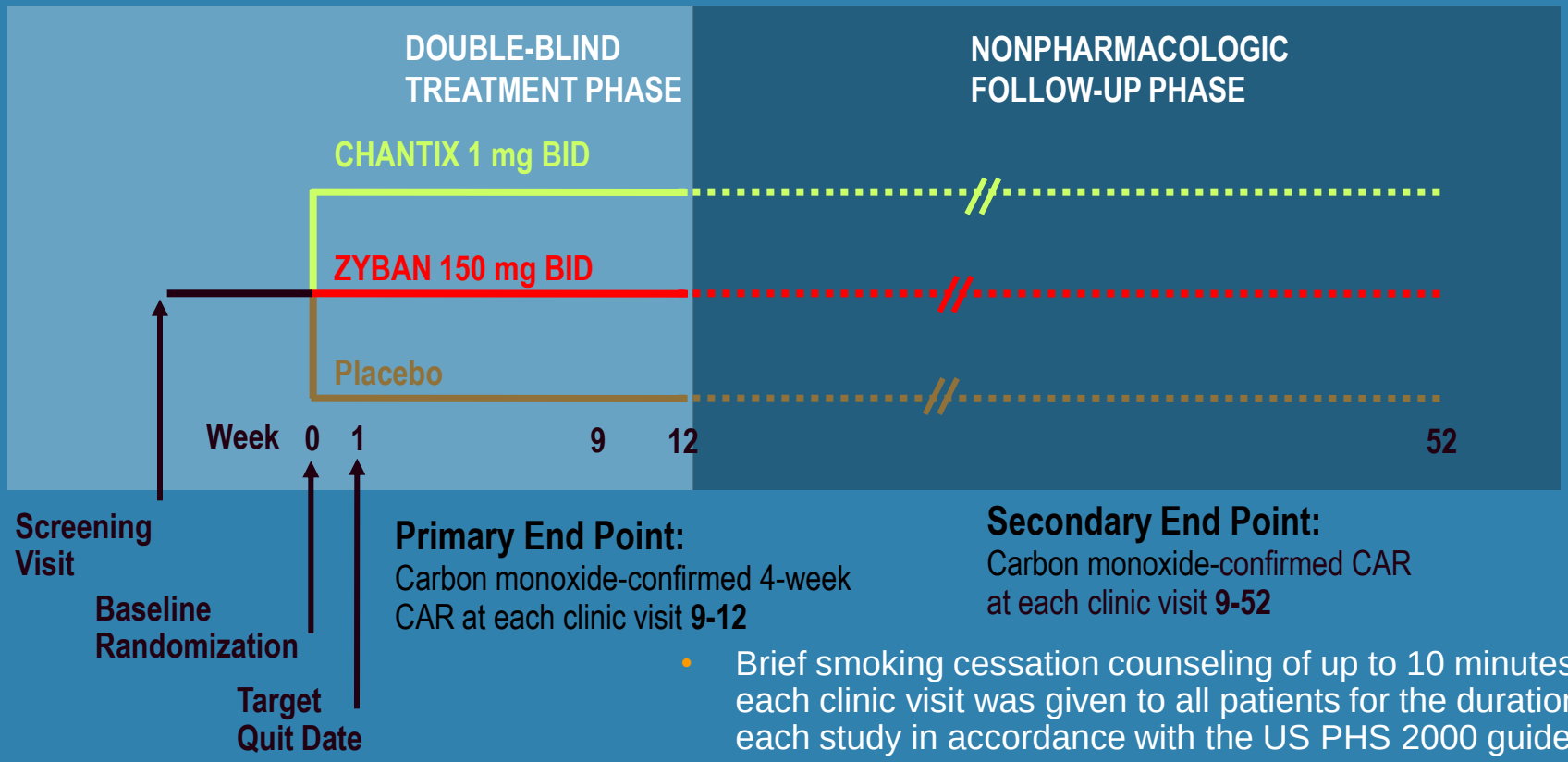
- CHANTIX competitively binds to α4β2 nicotinic receptors in the brain
  - Receptors play a key role in mediating reinforcement- and dependence-producing effects of nicotine
  - CHANTIX is a partial agonist at nicotinic receptors and a non-nicotine agent

Based on animal models and *in vitro* studies. For illustrative purposes only.

Chantix [package insert]. New York, NY: Pfizer Inc; July 2009.
Cordero-Erausquin M et al. *Trends Pharmacol Sci*. 2000;21:211-217.
Tapper AR et al. *Science*. 2004;306:1029-1032.
Picciotto MR et al. *Nature*. 1998;391:173-177.

Please see full Prescribing Information and Medication Guide on the following pages.

The Study Design of 2 CHANTIX® (varenicline) Pivotal Efficacy Studies



Primary End Point:
Carbon monoxide-confirmed 4-week CAR at each clinic visit **9-12**

Secondary End Point:
Carbon monoxide-confirmed CAR at each clinic visit **9-52**

- Brief smoking cessation counseling of up to 10 minutes at each clinic visit was given to all patients for the duration of each study in accordance with the US PHS 2000 guidelines

BID=twice daily; CAR=continuous abstinence rates; PHS=public health service.

Gonzalez D et al. *JAMA*. 2006;296(1):47-55; Jorenby DE et al. *JAMA*. 2006;296(1):56-63; Fiore MC et al. *US DHHS. Public Health Service*; 2000.
Jorenby DE et al. *JAMA*. 2006;296(1):56-63.
Fiore MC et al. www.surgeongeneral.gov/tobacco/default.html. Accessed October 2, 2007.
Chantix [package insert]. New York, NY: Pfizer Inc; 2007.

Please see full Prescribing Information and Medication Guide on the following pages.

Key Inclusion/Exclusion Criteria in the 2 CHANTIX® (varenicline) Pivotal Efficacy Studies

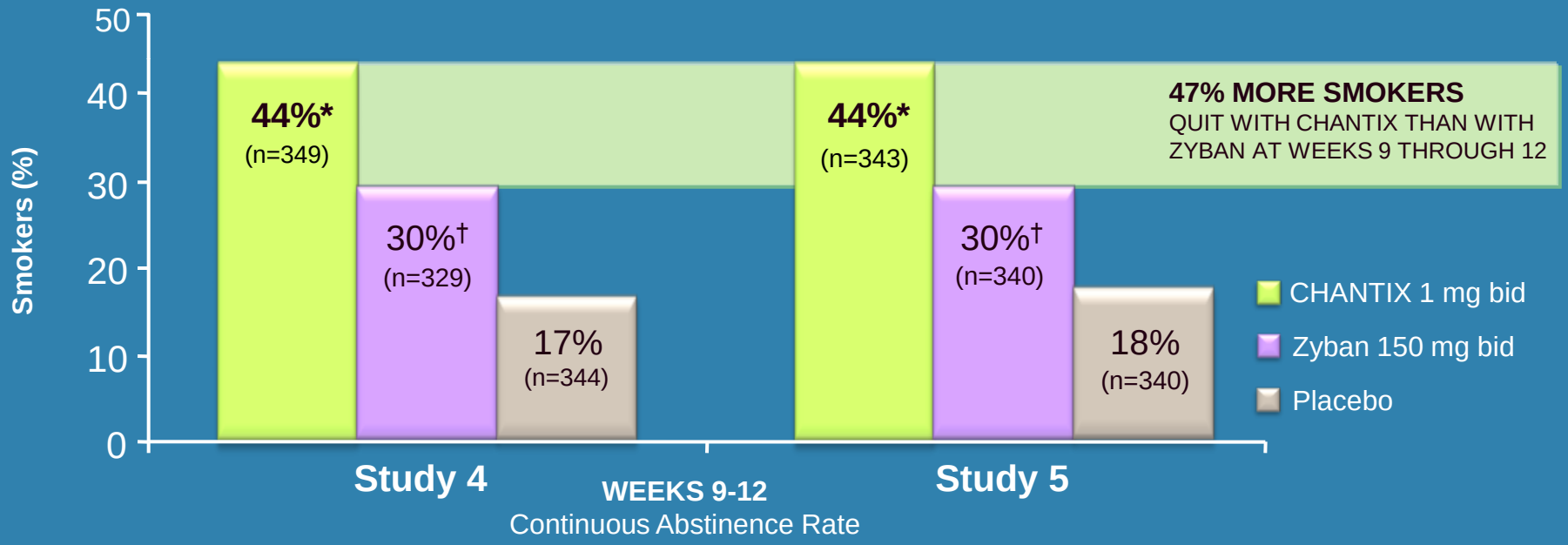
- Male or female outpatient cigarette smokers
- Aged 18 to 75 years
- Motivated to quit smoking
- ≥10 cigarettes each day during the past year and over the month prior to screening
- No period of abstinence >3 months in the past year
- Free of serious or unstable disease within past 6 months (eg, those with unstable CVD or a diagnosis of severe COPD were excluded)
- No previous use of bupropion or bupropion sustained release (SR) or contraindication for use of bupropion SR
- No other smoking cessation products within the past month
- Patients with treatment for major depression in the previous 12 months or history of current panic disorder, psychosis, or bipolar disorder were excluded

Gonzales D et al. *JAMA*. 2006;296(1):47-55.
Jorenby DE et al. *JAMA*. 2006;296(1):56-63.

Please see full Prescribing Information and Medication Guide on the following pages.

In These 2 CHANTIX® (varenicline) Pivotal Efficacy Studies (bupropion), Quit Rates With CHANTIX Were Superior to Zyban® During Weeks 9 Through 12

Two randomized placebo-controlled, double-blind studies:



- Trial evaluated CARs—ie, the percentage of all subjects treated who did not smoke (not even a puff of a cigarette)—during weeks 9 through 12
  - CARs for both CHANTIX and Zyban were superior to placebo

* *P*=0.0001 vs Zyban; *P*<0.0001 vs placebo.

† *P*=0.0002 vs placebo.

CHANTIX studies' primary efficacy end point was 4-week CAR, whereas many other studies used a 7-day PPA.

Zyban is a registered trademark of GlaxoSmithKline.

Chantix [package insert]. New York, NY: Pfizer Inc; July 2009.

Data on file. Pfizer Inc, New York, NY.

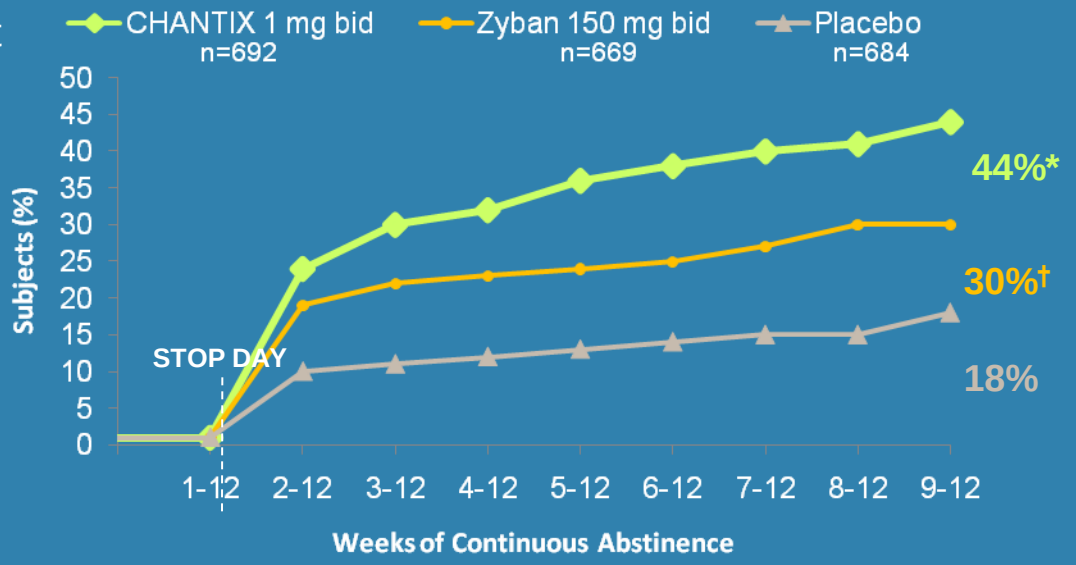
FDA. http://www.fda.gov/cder/foi/nda/2006/021928_s000_Chantix_StatR.pdf. Accessed August 25, 2006.

Please see full Prescribing Information and Medication Guide on the following pages.

Quit Rates Increased Over 12 Weeks

In a post hoc pooled analysis of 2 head-to-head pivotal trials, percentage of successful quitters increased during the 12-week course of treatment.

- CHANTIX® (varenicline) cumulative quit rates at weeks 9 through 12 were:
  - Higher at the 9-through-12-week time point vs all earlier time points
  - Superior to Zyban® (bupropion) and placebo
- Patients should be encouraged to continue their quit attempt even if they slip up and smoke during treatment, because some patients may successfully quit smoking later in the course of therapy
- A 3-month (12-week) course of CHANTIX is recommended



*P<0.0001 vs Zyban; P<.0001 vs placebo.

†P<0.0001 vs placebo.

STOP DAY=day subjects intended to stop smoking.

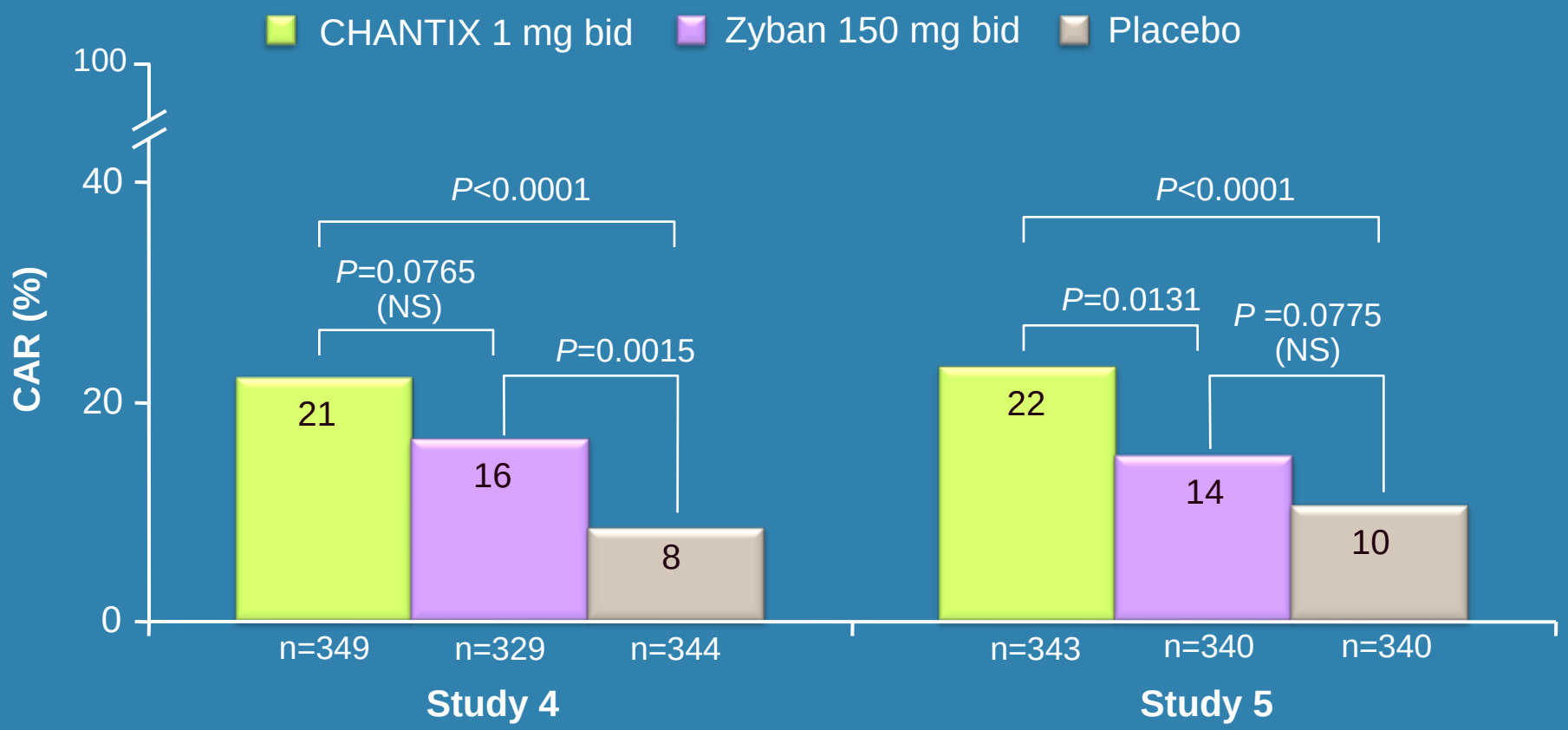
A post hoc analysis of pooled data from pivotal studies 4 and 5 from the CHANTIX package insert. Continuous abstinence was defined as the percentage of subjects who reported no smoking (not even a puff) or use of any nicotine-containing products confirmed by an exhaled carbon monoxide measurement of 10 ppm or less at each weekly clinic visit. **Subjects were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each clinic visit in accordance with Agency for Healthcare Research and Quality guidelines.**

Data on file. Pfizer Inc. New York, NY.

Chantix [package insert]. New York, NY: Pfizer Inc; 2008.

Please see full Prescribing Information and Medication Guide on the following pages.

In These 2 CHANTIX® (varenicline) Pivotal Efficacy Studies Abstinence Rates of CHANTIX Were Numerically Higher Than Zyban® in Weeks 9 to 52



CA is defined as no smoking (not even a puff) on multiple occasions throughout that defined period.
CA is based upon subject self-report confirmed by end-expiratory CO measurement (<10 ppm).
Zyban is a registered trademark of GlaxoSmithKline.

Chantix [package insert]. New York, NY: Pfizer Inc; July 2009.
Data on file. Pfizer Inc, New York, NY.
FDA. http://www.fda.gov/cder/foi/nda/2006/021928_s000_Chantix_StatR.pdf. Accessed August 25, 2006.

Please see full Prescribing Information and Medication Guide on the following pages.

Study 4: Treatment-Emergent Adverse Events*

n (%)	Varenicline n = 349	Bupropion SR n = 329	Placebo n = 344
Any adverse event	275 (79)	258 (78)	257 (75)
Gastrointestinal disorders			
Nausea	98 (28)	41 (13)	29 (8)
Dry mouth	23 (7)	29 (9)	19 (6)
Flatulence	20 (6)	14 (4)	10 (3)
Constipation	19 (5)	23 (7)	13 (4)
Psychiatric disorders			
Insomnia	49 (14)	72 (22)	44 (13)
Abnormal dreams†	36 (10)	18 (6)	19 (6)
Irritability	21 (6)	17 (5)	20 (6)
Sleep disorder	20 (6)	13 (4)	13 (4)
Nervous system disorders			
Headache	54 (16)	47 (14)	42 (12)
Dizziness	21 (6)	19 (6)	20 (6)
Respiratory system disorders			
Nasopharyngitis	20 (6)	17 (5)	18 (5)

* Treatment emergent adverse events were defined as those that began or increased in severity during study-drug treatment or up to 7 days after the last dose. Reported events occurred at 5% or more for varenicline and at a higher frequency that reported or placebo.

† Self-described as any change in dreaming, such as vivid dreams or increased frequency of dreaming.

Gonzales D, et al. for the Varenicline Phase 3 Study Group. *JAMA*. 2006;296:47-55.

Please see full Prescribing Information and Medication Guide on the following pages.

Study 5: Treatment Emergent Adverse Events*

n (%)	Varenicline (n = 343)	Bupropion SR (n = 340)	Placebo (n = 340)
Gastrointestinal disorders			
Nausea	101 (29)	25 (7)	33 (10)
Constipation	31 (9)	22 (7)	5 (2)
Flatulence	20 (6)	7(2)	8 (2)
Dry mouth	19 (6)	26 (8)	11(3)
Dyspepsia	19 (6)	10 (3)	12 (4)
Vomiting	18 (5)	7 (2.1)	6 (2)
Psychiatric disorders			
Insomnia	49 (14)	72 (22)	42 (12)
Abnormal dreams†	45 (13)	20 (6)	12 (4)
Sleep disorder	16 (5)	23 (7)	9 (3)
Anxiety	15 (4)	18(5)	13 (4)
Nervous system disorders			
Headache	44 (13)	27 (8)	43 (13)
Dizziness	22 (6)	25 (7)	24 (7)
Fatigue	25 (7)	13 (4)	22 (7)

SR= sustained release

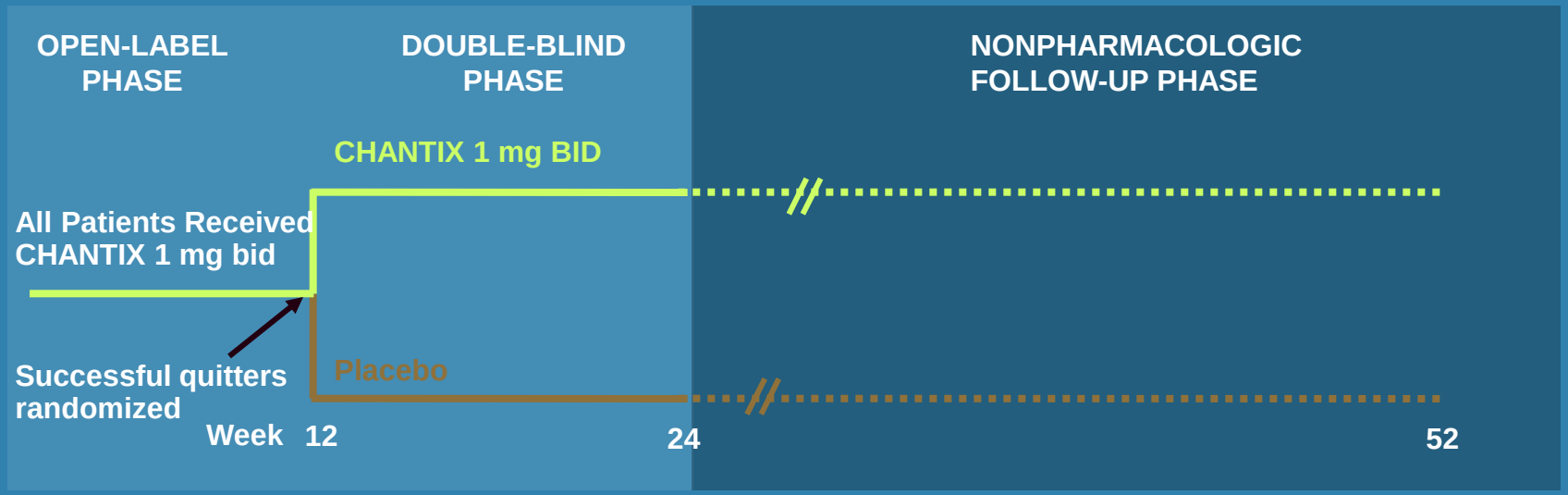
* Treatment emergent adverse events were defined as those that began or increased in severity during study-drug treatment or up to 7 days after the last dose. Reported events occurred at 5% or more for varenicline and at a higher frequency that reported or placebo.

† Self-described as any change in dreaming, such as vivid dreams or increased frequency of dreaming.

Jorenby DE, et al. for the Varenicline Phase 3 Study Group. *JAMA*. 2006;296:56-63.

Please see full Prescribing Information and Medication Guide on the following pages.

Design of CHANTIX® (varenicline) Maintenance of Abstinence Study



Primary end point:
Carbon monoxide-confirmed 4-week CAR at each clinic visit, weeks **13-24**

Secondary end point:
Carbon monoxide-confirmed CAR at each clinic visit, weeks **13 to 52**

- **Brief counseling of up to 10 minutes at each contact was given to all patients for the duration of the study, in accordance with the US PHS 2000 guidelines**

Tonstad S et al. *JAMA*. 2006;296(1):64-71; Fiore MC et al. US DHHS. Public Health Service; 2000.

Please see full Prescribing Information and Medication Guide on the following pages.

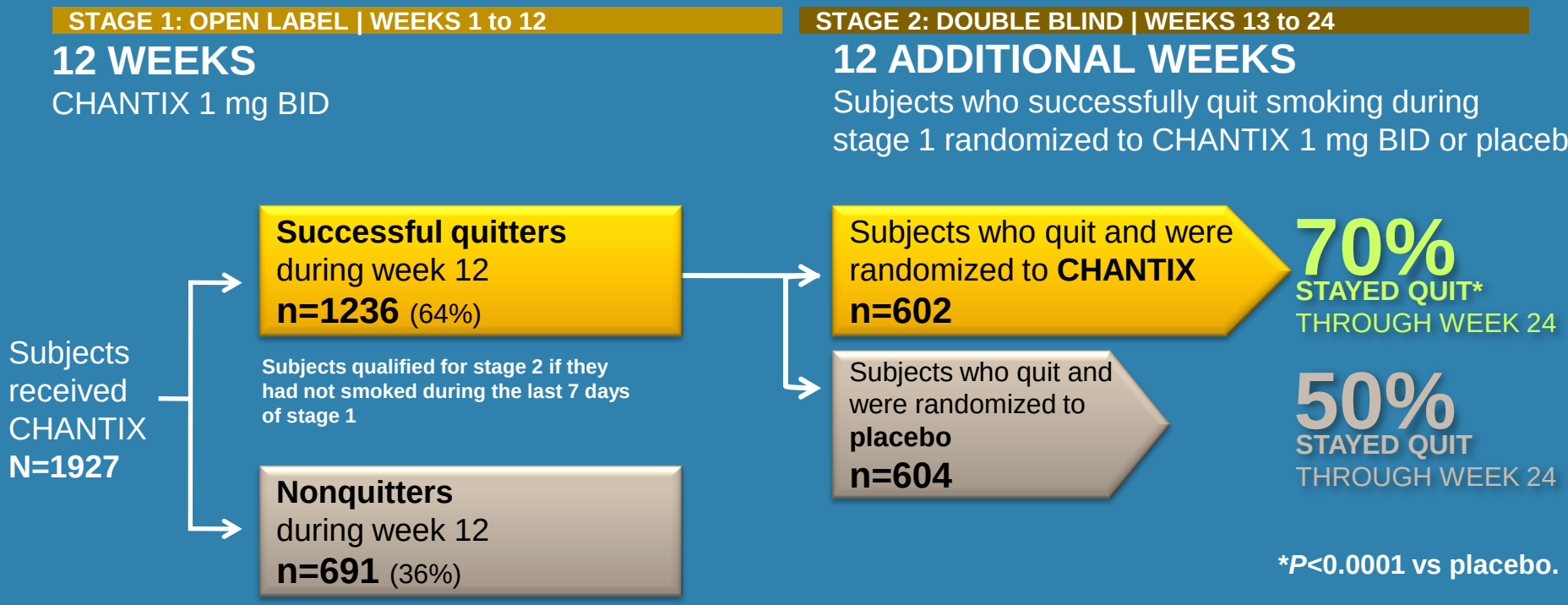
Key Inclusion/Exclusion Criteria in the CHANTIX® (varenicline) Maintenance of Abstinence Study

- Male or female outpatient cigarette smokers
- 18 to 75 years
- Motivated to quit smoking
- ≥10 cigarettes each day during the past year and over the month prior to screening
- No period of abstinence >3 months in the past year
- Free of serious or unstable disease within past 6 months (eg, those with unstable CVD or a diagnosis of severe COPD were excluded)
- No other smoking cessation products within the past month
- Patients with treatment for major depression in the previous 12 months or history of current panic disorder, psychosis, or bipolar disorder were excluded
- Same key inclusion criteria for all phase 3 studies (Study 4, 5, and maintenance of abstinence). The only difference is that the patients in the study did not have to be bupropion naive in the maintenance of abstinence study

Tonstad S et al. *JAMA*. 2006;296(1):64-71.

Please see full Prescribing Information and Medication Guide on the following pages.

The CHANTIX® (varenicline) Maintenance of Abstinence Study Helped Successful Quitters Remain Quit



- All subjects in stage 2 had successfully quit smoking with 12 weeks of therapy with CHANTIX during stage 1
  - Of these subjects, those who received 12 additional weeks of CHANTIX vs placebo during stage 2 were significantly more likely to remain quit at weeks 13 through 24

Tonstad S et al. *JAMA*. 2006;296(1):64-71.
Chantix [package insert]. New York, NY: Pfizer Inc; 2007.

Please see full Prescribing Information and Medication Guide on the following pages.

Study 6: Treatment-Emergent Adverse Events* During Smoking Cessation and Maintenance Therapy

n (%)	12-week open-label	12-week double-blind maintenance treatment phase	
	Varenicline (n = 1927)	Varenicline (n = 602)	Placebo (n = 604)
Gastrointestinal disorders			
Nausea	645 (34)	7 (1)	4 (1)
Flatulence	234 (12)	2 (<1)	0
Constipation	168 (9)	0	3 (<1)
Dyspepsia	133 (7)	9 (2)	6 (1)
Psychiatric disorders			
Insomnia	377(20)	16 (3)	17(3)
Abnormal dreams†	276 (14)	6 (1)	0
Irritability	97 (5)	16 (3)	27 (5)
Nervous system disorders			
Headache	304 (16)	17 (3)	12 (2)
Nasopharyngitis	145 (8)	29 (5)	32 (5)
Fatigue	162 (8)	9 (2)	11 (2)

* Treatment emergent adverse events were defined as those that began or increased in severity during study-drug treatment or up to 7 days after the last dose. Reported events occurred at 5% or more for varenicline and at a higher frequency that reported or placebo.

† Self-described as any change in dreaming, such as vivid dreams or increased frequency of dreaming.

Tonstad S, et al. for the Varenicline Phase 3 Study Group. *JAMA*. 2006;296:64-71.

Please see full Prescribing Information and Medication Guide on the following pages.

CHANTIX® (varenicline) Is Provided in a Starting-Month Pak and a Continuing Pak, to Encourage Proper Use

1 starting-month pak (4 weeks)

2 continuing-months paks (4 weeks each)

3 continuing-months paks (4 weeks each) for patients who successfully quit with 12 weeks of CHANTIX. An additional 12 weeks—for a total of 24 weeks—of therapy is recommended to help them remain smoke free

- Patients should begin taking CHANTIX 1 week before they intend to stop smoking
- Some patients may experience nausea while taking CHANTIX; CHANTIX should be taken after eating and with a full glass of water
- CHANTIX 0.5- and 1-mg tablets are also available in bottles to accommodate patients who require dosage adjustment

The most common adverse reactions include nausea, sleep disturbance, constipation, flatulence, and vomiting. Nausea occurred in 30% of patients, while 3% discontinued due to nausea.

Please see full Prescribing Information and Medication Guide on the following pages.

Pharmacokinetic Properties of CHANTIX® (varenicline)

- Absorption
  - Very water-soluble molecule
  - C_{max}: 3 to 4 h
  - Food has no effect on pharmacokinetics
  - Time-of-day dosing has no effect
  - Dose proportionality of PK
- Distribution
  - Plasma protein binding of CHANTIX is low (≤20%) and independent of age or renal function
- Metabolism
  - 92% is excreted as unchanged drug in the urine
  - No inhibition of the cytochrome P450 pathway shown in vitro
  - No clinically meaningful pharmacokinetic drug-drug interactions have been identified
- Excretion
  - Long half-life: approximately 24 hours

PK=pharmacokinetics.

Chantix [package insert]. New York, NY: Pfizer Inc; 2008.

Please see full Prescribing Information and Medication Guide on the following pages.

GETQUIT
Behavioral Modification Program

Please see full Prescribing Information and Medication Guide on the following pages.

Even With Treatment, Smoking Cessation Presents Difficult Physical and Psychological Challenges

Physical Challenges
When they smoke: Smokers experience reward/satisfaction due to increased dopamine release; this encourages them to keep smoking. When they stop smoking: Smokers experience craving and withdrawal symptoms that drive them to smoke again.

Psychological Challenges
Daily activities—such as having a morning cup of coffee or taking a break at work—may trigger the desire to smoke.

Pharmacotherapy

Counseling

US Department of Health and Human Services Clinical Guidelines:

Pharmacotherapy along with **counseling** is recommended for adult smokers trying to quit.*

- Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day
- Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms

* Special consideration should be given before using pharmacotherapy with selected populations: those with medical contraindications, those smoking fewer than 10 cigarettes per day, pregnant/breast-feeding women, and adolescent smokers.

Please see full Prescribing Information and Medication Guide on the following pages.

GETQUIT™ Support Plan: Behavioral Modification Program Available to CHANTIX® (varenicline) Users

Developed by Smoking Cessation Experts

Designed to help manage the physical, psychological, and social challenges of quitting on a daily basis, including:

- Educating smokers to recognize and manage behavioral components of smoking and triggers that lead to slip-ups and relapses
- Providing social, problem-solving, and product support throughout the quitting process
- Complementing clinicians' counseling role with patients

Available to all patients using CHANTIX at no additional cost

Please see full Prescribing Information and Medication Guide on the following pages.

The GETQUIT Approach Is Tailored to Individual Patients' Needs

- Program delivered through a multichannel approach
  - Online (daily e-mails and Web site with helpful topics and activities)
  - Telephone (inbound interactive voice response [IVR], daily automated messaging, nightly check-in calls)
  - Direct mail of printed program materials for offline users
- Content customized to each enrolled patient
  - Delivery of components tailored to each enrollee to meet lifestyle needs
  - Content tailored to provide personalized support reflecting personal habits and compliance with drug therapy and program, and to provide encouragement to help patients remain smoke free
- Interaction designed for optimal intervention and support
  - Daily interactions during first 5 weeks, when quitting is most difficult
  - Weekly interactions per week during the maintenance stage, through week 52
  - Maintenance support offered for up to 1 year after enrollment
- Includes access to Mayo Clinic-trained and-certified tobacco cessation specialists, 7 days per week

Please see full Prescribing Information and Medication Guide on the following pages.

GETQUIT Support Plan: A Day in the Life

- During the course of the program, participants will receive support and information in the morning via an automated call or the Web

TOPIC OF THE DAY

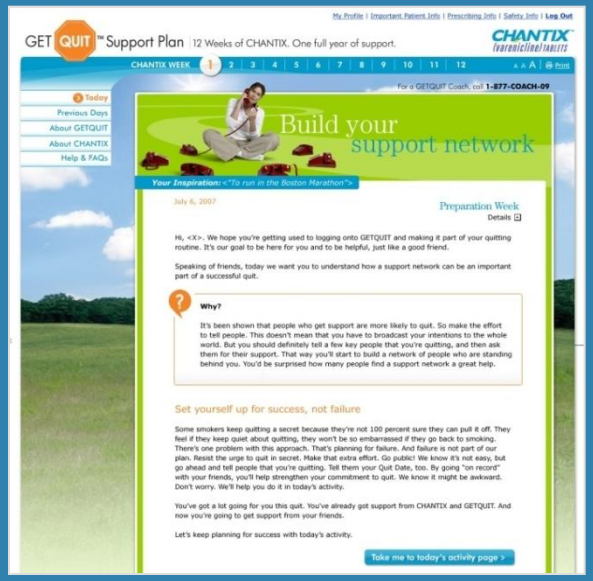
The topic delivered is based upon the user's stage in the quit process, to ensure content is relevant

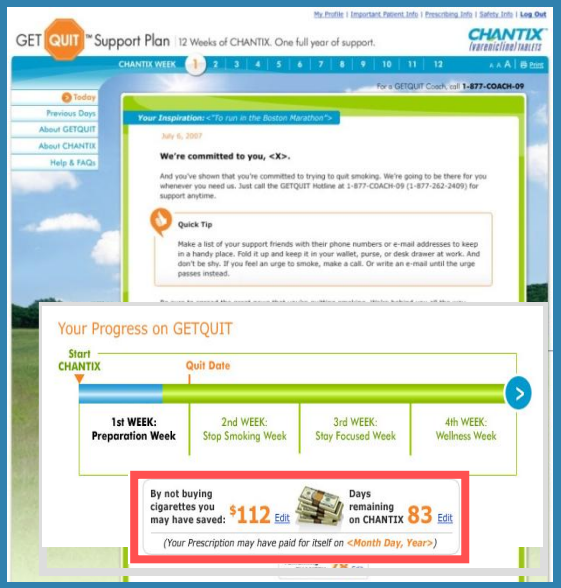
ACTIVITY

Reinforces topics and helps users take actions to help them recognize and change their behaviors

RECAP

Delivers reinforcement on program engagement and progress, quit status, money saved, and adherence

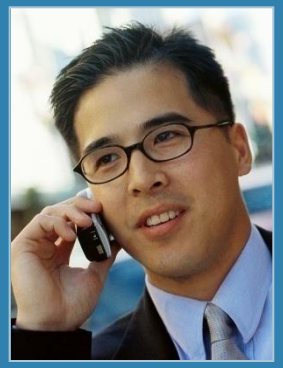




Please see full Prescribing Information and Medication Guide on the following pages.

GETQUIT Support Plan: Patients Can Opt-In For Support

Good evening, Steve. Have you smoked since your last check in?



- Participants can opt for an automated check-in call each evening
- Each night, participants receive a quick automated “check-in call” at the time of their choice (this call is available for online or offline participants)
- Nightly check-in ensures participants are held responsible for their actions and provides an added incentive to stay smoke free
- For participants who remain smoke free, dynamic content delivered through their morning topic/activity/recap messages recognizes and rewards them for accomplishments
- For participants who slip up, participant response triggers interventions designed to help prevent slip-ups from becoming relapses

Please see full Prescribing Information and Medication Guide on the following pages.

GETQUIT Support Plan: Patients Can Proactively Seek Guidance From Trained Professionals

Users can also proactively contact GETQUIT for support:

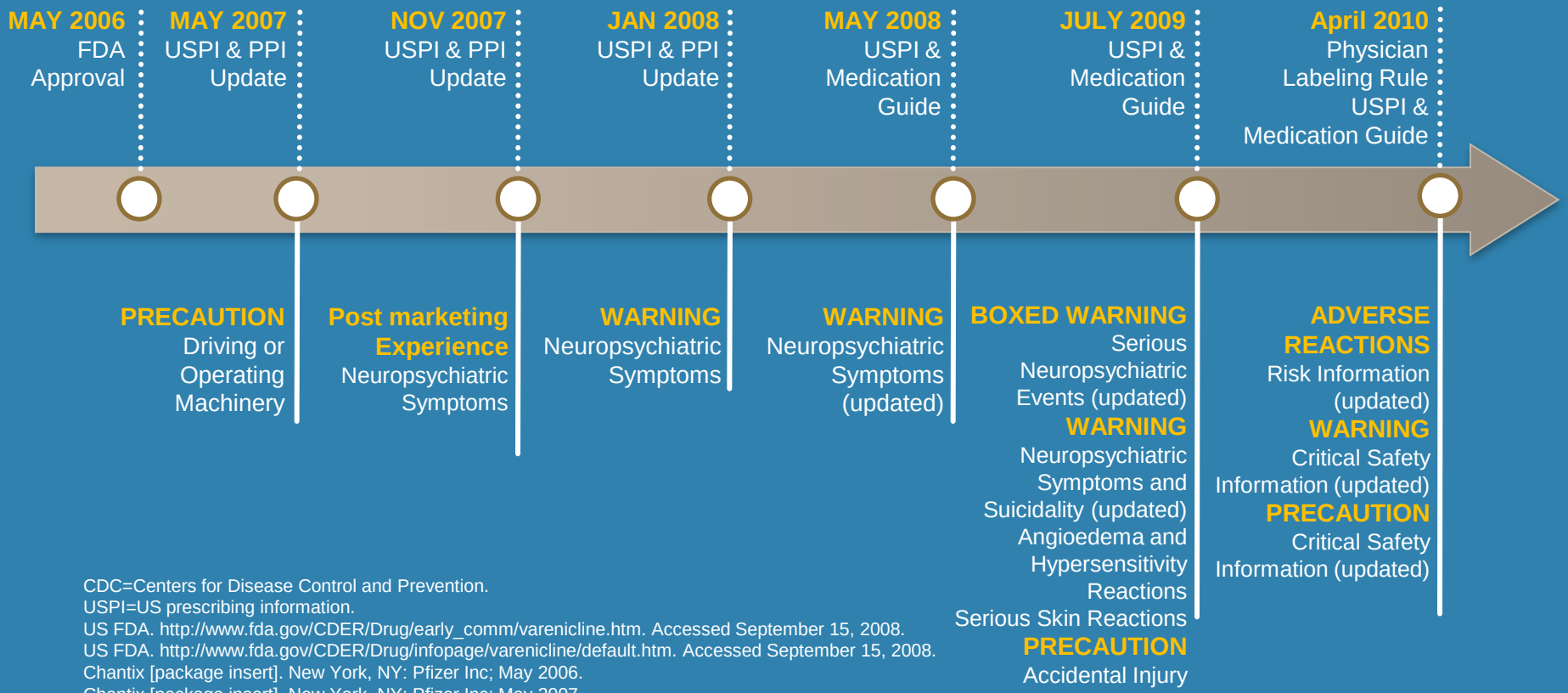
- Dedicated 24/7 GETQUIT hotline exclusively for GETQUIT enrollees
- 8:00 AM-12:00 AM, 7 days per week
  - GETQUIT coaches are available. These coaches are trained and certified by the Mayo Clinic as smoking cessation counselors who leverage motivational interviewing techniques
- 24 hours per day, 7 days per week
  - Prerecorded messages, created by psychologists to help users overcome stress, lack of motivation, or negative effects (eg, disappointment in oneself), are available

MAYO CLINIC

Please see full Prescribing Information and Medication Guide on the following pages.

Safety Information

Updates to CHANTIX® (varenicline) US Labeling: 2007-2009



CDC=Centers for Disease Control and Prevention.
USPI=US prescribing information.

US FDA. http://www.fda.gov/CDER/Drug/early_comm/varenicline.htm. Accessed September 15, 2008.
US FDA. http://www.fda.gov/CDER/Drug/infopage/varenicline/default.htm. Accessed September 15, 2008.
Chantix [package insert]. New York, NY: Pfizer Inc; May 2006.
Chantix [package insert]. New York, NY: Pfizer Inc; May 2007.
Chantix [package insert]. New York, NY: Pfizer Inc; November 2007.
Chantix [package insert]. New York, NY: Pfizer Inc; January 2008.
Chantix [package insert]. New York, NY: Pfizer Inc; May 2008.
Chantix [package insert]. New York, NY: Pfizer Inc; July 2009.
Chantix [package insert]. New York, NY: Pfizer Inc; [April] 2010.

Please see full Prescribing Information and Medication Guide on the following pages.

Updates to CHANTIX® (varenicline) US Labeling: July 2009 –*Boxed Warning*

WARNING:

Serious neuropsychiatric events, including, but not limited to depression, suicidal ideation, suicide attempt and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking CHANTIX in the post-marketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

(See **WARNINGS/Neuropsychiatric Symptoms and Suicidality, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Post-Marketing Experience**)

Chantix [package insert]. New York, NY: Pfizer Inc; July 2009.

Please see full Prescribing Information and Medication Guide on the following pages.

CHANTIX® (varenicline) USPI Information About Post-marketing AE Reporting

- "The following adverse events have been reported during post-approval use of CHANTIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure"

Chantix [package insert]. New York, NY: Pfizer Inc; July 2009.

Please see full Prescribing Information and Medication Guide on the following pages.

The Role of Post-marketing AE Reporting

- Spontaneous post-marketing AE reports are useful in detecting potential product issues that warrant further investigation
  - Their utility lies in hypothesis generation to prompt exploration of possible explanations for the AE in question
- These post-marketing AE reporting programs potentially maintain ongoing safety surveillance of medications across all types of patients
- Participation enables health care professionals to contribute to improving public health

Goldman SA. Limitations and strengths of spontaneous reports data. *ClinTher.1998;20 (suppl C):C40-44*.

Please see full Prescribing Information and Medication Guide on the following pages.

Interpretation of Post-marketing AE Reporting

- There are serious and well-recognized limitations to spontaneous post-marketing AE reporting. These limitations include the following:
  - Critical factual information (eg, when/how long the medication was taken, the patient's medical history, concomitant medications, smoking status) is often missing
  - The peak rate of spontaneous AE reporting for a medication often occurs within 2 or 3 years of marketing, with a subsequent decline in reporting
  - Because these reports are voluntary and unsolicited, there is the potential for under-reporting,over-reporting, and duplication of reporting
  - AE reporting may increase as a result of media coverage, labeling changes, or other external influences (ie, "stimulated" reporting)
- Interpretation of some neuropsychiatric AEs (eg depression, suicide) is complicated because of known background rates in smokers and some are known symptoms of nicotine withdrawal (eg, depressed mood, anxiety)
- In collaboration with the FDA, Pfizer continually reviews this information and updates the Prescribing Information as appropriate

Weber JCP. In: Rainsford KD, Velo GP, eds. *Advances in Inflammation Research*. Vol 6. New York, NY: Raven Press;1984:1-7.

Please see full Prescribing Information and Medication Guide on the following pages.

Nicotine Has Powerful Effects on Smokers

- The addictive characteristics of nicotine are a result of the speed of its action and the pleasurable effects of dopamine release in the brain
- In spite of known health risks, many adults continue to smoke
  - In the United States, more than 45 million adults are current cigarette smokers (nearly 21% of the adult population). In some subpopulations, smoking prevalence is higher
- Age-adjusted prevalence of smoking by disease or disorder
  - Psychiatric disorders*: **22% to 90%**
  - Respiratory disease: **41% to 49%**
  - Cancer (other than lung)†: **39%**
  - Cardiovascular disease‡: **29% to 30%**
  - Diabetes: **24%**
  - Lung cancer: **21%**

Cigarette smoking is the leading preventable cause of disease and premature death in the United States.

* Smoking prevalence rates in patients with specific psychiatric disorders have been reported as 45% to 90% for schizophrenia, 22% to 60% for depression, 51% to 70% for bipolar disorder, and up to 66% for posttraumatic stress disorder.

† Includes cancers of the bladder; cervix; esophagus; kidney; larynx-windpipe; mouth, tongue, or lip; pancreas; stomach; and throat-pharynx.

‡ Includes coronary heart disease, angina pectoris, myocardial infarction, and stroke.

Anthenelli RM. *ClinNeurosci Res*. 2005;5:175-183.
CDC. *MMWR Morb Mortal Wkly Rep*. 2007;56:1157-1161.
Kalman D et al. *Am J Addict*. 2005;14:106-123.
Williams JM, Ziedonis D. *Addict Behav*. 2004;29:1067-1083.
Ford ES, et al. *Prev Med*. 2004;39:1238-1242.

Smoking Cessation, With or Without Treatment, Is Associated With Nicotine Withdrawal Symptoms

- Nicotine withdrawal symptoms may cause clinically significant distress and impair social, occupational, or other important areas of function
- Common nicotine withdrawal symptoms include:
  - Urge to smoke
  - Dysphoric or depressed mood
  - Insomnia
  - Irritability, frustration, or anger
  - Anxiety
  - Difficulty concentrating
  - Restlessness
  - Decreased heart rate
  - Increased appetite or weight gain
- As with all medications, people taking smoking cessation medications may experience adverse events

APA. *DSM-IV. Text revision*. 1994:175-273.
USDHHS. *The Health Benefits of Smoking Cessation: a Report of the Surgeon General*. 1990.
US FDA. http://www.fda.gov/cder/info/consumer_safety.htm. Accessed November 25, 2008.

Incidence of Selected Psychiatric Adverse Events* Based on Post Hoc Analysis of Pooled Data From 10 CHANTIX® (varenicline) Placebo-Controlled RCTs†

Psychiatric Disorders High Level Group Terms (example preferred terms)	CHANTIX (≤1mg bid) n=3091		Placebo n=2005	
	n	% incidence	n	% incidence
Anxiety disorders and symptoms	138	4.5%	101	5.0%
Changes in physical activity (including restlessness)	33	1.1%	20	1.0%
Depressed mood disorders and disturbances (including depressed mood, depression, depressive symptoms)	88	2.8%	38	1.9%
Disturbances in thinking and perception (including hallucination)	13	0.4%	2	0.1%
Manic and bipolar mood disorders and disturbances	2	0.1%	0	0.0%
Mood disorders and disturbances (including anger, apathy, frustration)	73	2.4%	30	1.5%
Personality disorders and disturbances in behavior (including aggression, hostility)	5	0.2%	5	0.2%
Schizophrenia and other psychotic disorders	1	<0.1%	1	0.1%
Suicidal and self-injurious behaviors (suicidal ideation, suicide attempt)	0	0.0%	2	0.1%

* Disorders selected on the basis of incidence (>1% in the CHANTIX group) or clinical relevance; sleep disorders are excluded.
Relative Risks (RRs) and their 95% confidence intervals were calculated for the categories of adverse events shown for Chantix vs placebo applying a protocol stratification. For all RRs, the 95% CI crossed 1.

† Placebo-controlled RCTs completed as of March 31, 2009.

Tonstad S, et al. *Drug Saf.* 2010;33:289-301.

Please see full Prescribing Information and Medication Guide on the following pages.

Participants With History of Depression Not Requiring Treatment in Previous 12 Months

Examination of a subpopulation of participants with a history of depression (4.7% of CHANTIX® [varenicline] and 5.1% of placebo subjects) enrolled in the randomized clinical trials showed no evidence that treatment with CHANTIX conferred any additional risk (compared with placebo) of depression-related events

Number and percentage of participants with a history of depression who reported new onset or worsening of depression-related events

	CHANTIX (≤1mg bid) n=3091	Placebo n=2005
Number of participants with depressed mood disorders and disturbances in medical history	145	103
Number (%) of participants with history of depression who reported new onset or worsening of depression-related events	13 (9.0%)	9 (8.7%)

Results based on the same 10 randomized, double-blind, placebo-controlled trials, as on previous slide.
Analysis of the participants with history of depressed mood disorders and disturbances. MedDRA 11.0

1. Data on file. Pfizer Inc, New York, NY.
2. Tonstad S, et al. *Drug Saf.* 2010;33:289-301.

Please see full Prescribing Information and Medication Guide on the following pages.

Important Safety Information

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking CHANTIX in the post-marketing experience.

These events have occurred in patients with and without pre-existing psychiatric disease; patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

Patients should be advised to stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

Chantix [package insert]. New York, NY: Pfizer Inc; [April] 2010.

Please see full Prescribing Information and Medication Guide on the following pages.

Important Safety Information (cont'd)

Indication
CHANTIX is indicated as an aid to smoking cessation treatment in adults 18 and over. Patients may benefit from behavioral modification and support during their quit attempt. Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.

Important Safety Information
CHANTIX is contraindicated in patients with a history of serious hypersensitivity or skin reactions to CHANTIX.

Some people can have serious skin reactions while taking CHANTIX, some of which can become life threatening. These can include rash, swelling, redness, and peeling of the skin. Some people can have allergic reactions to CHANTIX, some of which can be life-threatening and include: swelling of the face, mouth, and throat that can cause trouble breathing. If patients experience these symptoms or a rash with peeling skin or blisters in the mouth, they should be advised to stop taking CHANTIX and get medical attention right away.

The most common side effects include nausea (30%), sleep problems, constipation, gas, and/or vomiting. Patients may have trouble sleeping, vivid unusual or strange dreams while taking CHANTIX. Patients should use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

Safety and efficacy of CHANTIX in combination with other smoking cessation drug therapies have not been studied. A lower dose of CHANTIX may be necessary in patients with kidney problems or who get dialysis.

Before starting CHANTIX, patients should tell their doctors if they are pregnant, plan to become pregnant, or if they take insulin, asthma medicines, or blood thinners. Medicines like these may work differently when patients quit smoking.

Chantix [package insert]. New York, NY: Pfizer Inc; [April] 2010.

Please see full Prescribing Information and Medication Guide on the following pages.

Summary

Summary and Conclusions

- **Smoking not only serves as a risk factor for a number of chronic diseases, but it also results in additional lifetime medical expenses/person and days lost from work for smokers, compared with nonsmokers**
- **Smoking is a chronic, relapsing medical condition**
- **Multiple organizations support smoking cessation coverage for patients attempting to quit smoking and recommend that they be offered effective pharmacotherapy along with counseling**
- **CHANTIX® (varenicline) is a dual-action agent specifically designed for smoking cessation in adults ≥18 years**
- **CHANTIX has been demonstrated to be effective as an aid to smoking cessation treatment and its tolerability and safety profile has been studied in over 4500 CHANTIX patients in efficacy and safety studies**
  - The CHANTIX labeling has been updated to include a boxed warning about reports of neuropsychiatric events, an updated warning about reports of neuropsychiatric symptoms and suicidality, warnings about reports of angioedema/hypersensitivity reactions and serious skin reactions, and a precaution about reports of accidental injury
- **Through March 2009, CHANTIX has been prescribed to approximately 11 million patients worldwide and approximately 6.9 million patients in the United States**
- **The GETQUIT Plan is designed to provide ongoing support and encouragement to help patients face the day-to-day challenges of quitting**
- **Smoking cessation is a valuable benefit that can help reduce overall health care costs and improve productivity**
- **Providing a comprehensive program for smoking cessation may help increase quit attempts**

IMS Midas data; July ’06 to March ’09.

Please see full Prescribing Information and Medication Guide on the following pages.

Pfizer U.S.Pharmaceuticals